VA Palo Alto Health Care System
Stanford University School of Medicine

Mailing Address:
Anesthesiology Service (112A)
Veterans Affairs Palo Alto Health Care System
3801 Miranda Avenue
Palo Alto, CA 94304

STEVEN L. SHAFER, MD
PROFESSOR OF ANESTHESIA
STANFORD UNIVERSITY
ADJUNCT PROFESSOR OF BIOPHARMACEUTICAL SCIENCE
UNIVESITY OF CALIFORNIA at SAN FRANCISCO

PHONE (650) 852-3419
FAX (650) 969-3315
MOBILE (650) 704-0558
E-MAIL Steven.Shafer@stanford.edu
WWW anesthesia.stanford.edu/pkpd

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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition
Bioequivalence for Transdermal Fentanyl

Dear FDA Officer:

The undersigned submits this petition under the generic bioequivalence guidelines of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10) to request the Commissioner of Food and Drugs to request specific action on the regulation of generic transdermal fentanyl delivery systems, and to request similar attention to new product approvals for transdermal fentanyl products.

A. Action requested

My request to the agency is twofold:

1) For any generic transdermal fentanyl product, the applicant should be required to demonstrate bioavailability / bioequivalence against Duragesic on both intact skin and on skin in which the stratum corneum has been stripped.

2) For any new fentanyl formulation, either from the innovator company (Alza) or a competitor, safety must be demonstrated when the device is placed on stripped skin.

B. Statement of grounds

The stratum corneum is a layer of dead, desiccated skin cells on the outermost surface of the skin. The stratum corneum poses a significant barrier to the movement of fentanyl from a transdermal delivery system, such as Duragesic, into the systemic circulation. The stratum

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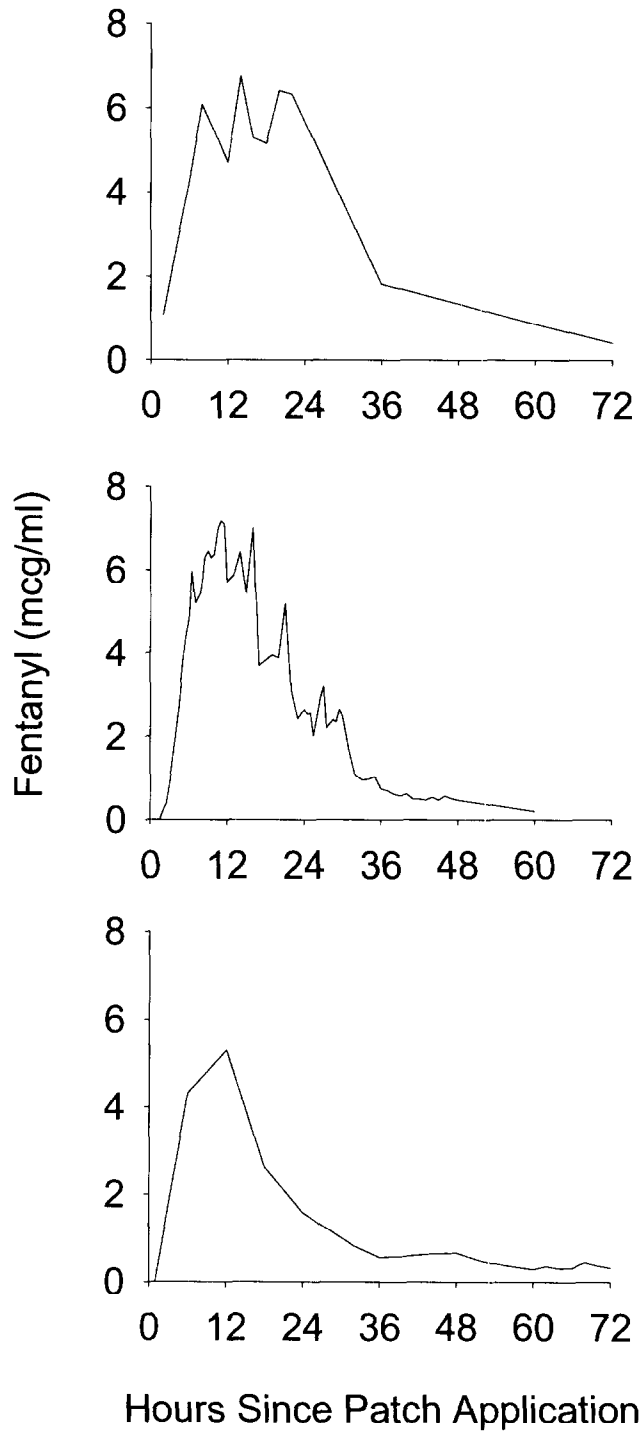
corneum is readily removed by such simple maneuvers as applying tape to the skin and pealing the tape off. It is not possible to visually distinguish normal skin with intact stratum from skin in which the stratum corneum is stripped. However, fentanyl will flow from a transdermal system into the systemic circulation far more rapidly across stripped skin than across skin with intact stratum corneum.

The existing Duragesic product has a rate limiting membrane that is intended to provide approximately equal resistance to skin penetration as intact skin.[1] As a result, the "worst case" rate of absorption in the event that the stratum corneum has been stripped from the skin is a doubling of the transfer rate. Other transdermal systems have been developed that lacked any intrinsic control of the rate of transdermal drug delivery. These systems relied exclusively on intact stratum corneum to control the rate of fentanyl delivery. These systems have demonstrated huge variability in fentanyl delivery rate and concentration, potentially exposing patients to toxic levels of fentanyl.[2]

This is not a theoretical concern. I have personally analyzed such data.[1,2] The figure to the right shows three fentanyl concentration curves from several studies conducted over a decade ago as part of the attempts by Cygnus corporation to obtain approval for a generic form of transdermal fentanyl. These volunteers experienced rapid absorption of fentanyl, and as a result their concentrations reach potentially toxic levels. Fortunately, these volunteers were well monitored, and were not injured by the high fentanyl concentrations. However, had these levels occurred in patients, the result could have been serious injury or death.

The Cygnus product had no rate controlling membrane. Although it generally performed well, as can be seen above occasionally it delivered a huge overdose. This was traced to the lack of a rate controlling membrane, and happened in the setting of stripped skin.



This type of aberrant behavior of transdermal delivery systems in that depend on the stratum corneum to control the rate of drug delivery was seen in about 5-10 percent of the subjects in the Cygnus trials.

The risk to patients is that it is not predictable when the device might be placed on stripped skin. In the hospital patients frequently have adhesive placed on their bodies (e.g., tape, ECG electrodes, "band-aids", etc). Removing such adhesive strips the stratum corneum, without leaving any visible evidence of the damage. Patients at home similarly apply band-aids, waxing, and other common practices will strip the stratum corneum. In both cases, the patient will be exposed to unexpectedly rapid delivery of transdermal fentanyl, unless the device contains a system to limit fentanyl delivery, as is the case with the original Duragesic fentanyl delivery system.

I believe the appropriate response by the Agency is to issue a guidance for generic approval of transdermal opioids. Such guidance would state that appropriate bioequivalent studies be performed on both intact skin and skin in which the stratum corneum has been intentionally removed with adhesive tape. If a generic product demonstrates bioequivalence in both settings, then it can reasonably be expected to be as safe as the innovator.

The closest existing guidance that I have found is "GUIDANCE FOR INDUSTRY: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products" dated December, 1999. While this guidance focuses on skin irritation testing, it correctly observes that "more severe skin irritation may affect the efficacy or safety of the product" (page 1). It further notes in footnote 2 that "this guidance does not address the bioequivalence studies that would be needed for a particular transdermal drug product. These will vary according to the active ingredient in the product. The Office of Generic Drugs (OGD) should be contacted with questions regarding bioequivalence studies." This document anticipates the need for Agency guidance about the influence of skin condition on efficacy and safety of transdermal delivery systems. My petition specifically relates to footnote 2. I am requesting that the Office of Generic Drugs require demonstration of bioequivalence on stripped skin for approval of generic transdermal opioid delivery systems.

By way of disclosure, I am:
1) Co-author/Senior Author of both of the attached references. Reference 1 remains the only bioavailability study of Duragesic.

2) Professor of Anesthesia at Stanford University

3) Professor of Biopharmaceutical Science at UCSF

4) A member of the Anesthesia and Life Sciences Drugs Advisory Committee to the FDA

5) An occasional consultant to Alza Corporation (< 8 hours/year).

C. Environmental impact

Not Applicable

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Sincerely,

References:

1. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR. Absorption characteristics of transdermally administered fentanyl. Anesthesiology. 1989 Jun;70(6):928-34.

2. Fiset P, Cohane C, Browne S, Brand SC, Shafer SL. Biopharmaceutics of a new transdermal fentanyl device. Anesthesiology. 1995 Sep;83(3):459-69.

Guidance for Industry

Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1999
OGD #

Guidance for Industry

Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1999
OGD #

TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY[1]

Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

I. INTRODUCTION

This guidance is intended to assist sponsors of abbreviated new drug applications (ANDAs) by recommending study designs and scoring systems that can be used to test skin irritation and sensitization during development of transdermal products.

To fully evaluate the equivalence of a transdermal product for an ANDA to a reference listed drug (RLD), skin irritation and sensitization should be assessed because the condition of the skin may affect the absorption of a drug from a transdermal system.[2] More severe skin irritation may affect the efficacy or safety of the product.

Transdermal products have properties that may lead to skin irritation and/or sensitization. The delivery system, or the system in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and safety evaluations in the context of large clinical trials generally associated with the submission of new drug applications (NDAs). Separate skin irritation and skin sensitization studies also are used for this purpose. These latter studies are designed to detect irritation and sensitization under conditions of maximal stress and may be used during the assessment of transdermal drug products for ANDAs.

II. STUDY DESIGNS

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products for an ANDA are delineated below. Other proposals for studies may be

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[1] This guidance has been prepared by the Office of Generic Drugs in conjunction with the Division of Dermatological and Dental Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on studies to assess skin irritation and sensitization of proposed generic transdermal drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] This guidance does not address the bioequivalence studies that would be needed for a particular transdermal drug product. These will vary according to the active ingredient in the product. The Office of Generic Drugs (OGD) should be contacted with questions regarding bioequivalence studies.

suggested, but potential applicants are advised to consult the Office of Generic Drugs about alternative study designs prior to the initiation of such a study.

A. Recommendations for a Cumulative Skin Irritation Study

1. Sample size: 30 subjects

2. Exclusion criteria: Dermatologic disease that might interfere with the evaluation of test site reaction

3. Duration of study: 22 days

4. Study design: A randomized, controlled, repeat patch test study that compares the test patch to the innovator patch. Placebo patches (transdermal patch without active drug substance) and/or high- and low-irritancy controls (e.g., sodium lauryl sulfate 0.1% and 0.9% saline) can be included as additional test arms.

5. Patch application: Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 hours (plus or minus 1 hour) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied.

   Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

6. Evaluations: Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

   Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. (See Appendix A for an example of a scoring system that can be used.) The percent adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

7. Data presentation and analysis: Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day.

The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed (see Appendix C).

B. Recommendations for a Skin Sensitization Study (Modified Draize Test)

1. Sample size: 200 subjects

2. Exclusion criteria:

   a. Dermatologic disease that might interfere with the evaluation of the test site reactions.

   b. Use of systemic or topical analgesics or antihistamines within 72 hours of study enrollment or systemic or topical corticosteroids within 3 weeks of study enrollment.

3. Duration of study: 6 weeks

4. Study design: A randomized, controlled study on three test products: the test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

5. Patch application: Test sites should be randomized among patients. The study is divided into three sequential periods:

   - Induction Phase: Applications of the test materials should be made to the same skin sites 3 times weekly for 3 weeks, for a total of 9 applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

     Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. (See Appendix A for an example of a scoring system that can be used.) The percent adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

- Rest Phase: The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

- Challenge Phase: The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48, and 72 hours after patch removal. (See Appendix A for an example of a scoring system that can be used.)

6. Data presentation and analysis: The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

   A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

C. Combined Studies

Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to that described for the skin sensitization study (see section B), except that patch application during the induction phase should be daily for 23 hours (plus or minus 1 hour) each day over 21 days.

APPENDIX A

Skin Irritation Scoring Systems

The following scoring system for irritation and/or sensitization reactions is included as an example of a scoring system that can be used for these studies. Other validated scoring systems can be used in quantifying skin reactions. The inclusion of this system should not be interpreted as an endorsement of the system by the Agency. It is provided as an example only.[3]

I. Dermal response:

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

II. Other effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all or part of the patch site
H = small petechial erosions and/or scabs

[3] This is the system used by Hill Top Research, Inc.

APPENDIX B

Adhesion Score

The following scoring system is included as an example of a scoring system that can be used for this type of study. Other validated scoring systems may be equally effective in quantifying comparative adhesion of transdermal systems. The inclusion of this system is not to be interpreted as an endorsement of the system by the Agency. It is provided as an example only.[4]

An estimate of the adherence of the transdermal system will be rated as follows:

0 = • 90% adhered (essentially no lift off of the skin)
1 = • 75% to < 90% adhered (some edges only lifting off of the skin)
2 = • 50% to < 75% adhered (less than half of the system lifting off of the skin)
3 = < 50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4 = patch detached (patch completely off the skin)

[4] This is the system used by Hill Top Research, Inc.

APPENDIX C

To be considered equivalent for a particular response, the average response for the generic (μ_T) should be between 80% and 125% of the average response for the innovator (μ_R). It is recommended that the response of the generic be equivalent to or better than the innovator. This implies a one-sided test.

For a variable for which low scores are better, such as mean irritation score or total cumulative irritation score, the hypotheses would be

$$H_0: \mu_T/\mu_R > 1.25$$
$$H_1: \mu_T/\mu_R \bullet 1.25$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 1.25\mu_R > 0$$
$$H_1: \mu_T - 1.25\mu_R \bullet 0$$

The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is, the 95% upper confidence bound) for the quantity $\mu_T - 1.25\mu_R$ is less than or equal to zero.

For a variable for which high values are better, such as time to removal score, the hypotheses would be

$$H_0: \mu_T/\mu_R < 0.80$$
$$H_1: \mu_T/\mu_R \bullet 0.80$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 0.80\mu_R < 0$$
$$H_1: \mu_T - 0.80\mu_R \bullet 0$$

The null hypothesis H_0 will be rejected in this case when the lower limit of the 90% confidence interval (that is, the 95% lower confidence bound) for the quantity $\mu_T - 0.80\mu_R$ is greater than or equal to zero.

In either case, if the null hypothesis H_0 is rejected the generic should be considered equivalent or better than the innovator.

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Patel, S.M., E. Patrick, and H.I. Maibach, 1976, "Animal, Human, and In Vitro Test Methods for Predicting Skin Irritation," *Dermatotoxicology*, Chpt. 33, 5th Ed., Eds. F.N. Marzulli, H.I. Maibach, Taylor, and Frances.